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(54) Title: ASSAY CARTRIDGE

(57) Abstract

A cartridge for holding an analytical sample during a diagnostic assay comprises a panel with a number of adjacent wells in its upper side. The wells have an upper opening and a lower opening, and the lower opening extends to the underside of the panel. A filter membrane extends across the lower openings of the wells so that liquids contained in the wells may be drawn through the filter, thereby concentrating suspended solids near the lower openings of the wells. The panel includes a supporting wall for supporting the panel on a non-integral, external surface, which does not form a part of the panel.

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ASSAY CARTRIDGE

FIELD OF THE INVENTION

This invention relates generally to assay cartridges having a plurality of aligned adjacent wells which are useful as reaction vessels for performing diagnostic tests in which a solid phase is to be separated from a liquid phase, and is particularly directed to assay cartridges which are adapted so that the liquid phase may be separated from the solid phase by drawing it through a filter membrane at a lower opening in the wells by means of a pressure differential.

BACKGROUND OF THE INVENTION

Assay cartridges which include a plurality of wells for performing diagnostic assays on samples are known. The present invention relates to a class of cartridges which are generally described in U.S. Patent No. 4,704,255 to Jolley. These cartridges are designed to perform assays of the type described in U.S. Patent No. 4,652,533, also to Jolley. (For purposes of the present disclosure, both of the above patents are incorporated herein by reference and made a part hereof.)

To perform such assays, a sample is inoculated into one or more of the wells in the cartridge. An immunoreactant selected for its ability to bind the analyte of interest is attached to a plurality of water insoluble particles held in a suspended state in reagent liquids. Upon introduction of the suspended particles and liquid into the sample wells, the immunoreactant selectively and/or competitively binds to analyte in the sample. The bottom of each well is covered with a filter membrane designed to retain the suspended particles while permitting liquids to pass through. The particles and any bound substrate are concentrated by microfiltration, that is, by drawing the liquids by means of a pressure differential through the membrane and into a waste reservoir, which is molded as an integral part of the cartridge. A luminescent labelled material which selectively binds to

the immunoreactant and/or the analyte is used to determine whether the analyte is present.

Although the assay cartridge described in U.S. Patent No. 4,652,533 has been used in performing assays of this type, there are several drawbacks associated with its manufacture and use. First, because the waste reservoir into which the fluids are drawn forms an integral part of the molded cartridge, the cartridge is difficult and relatively expensive to mold and requires a relatively large investment in tooling and a significant amount of material to manufacture. The complexity of the molding process also tends to increase yield losses due to improperly formed parts and excessive flash. Moreover, various subparts of the cartridge have been known to cool unevenly, resulting in warpage. In the most serious cases, warpage can hinder or even prevent the removal of liquid from the wells, thereby adversely affecting the performance of the cartridge in performing diagnostic assays. Finally, because the waste reservoir is molded integrally with the cartridge, it has been difficult to obtain a uniform vacuum draw underneath the wells. This, in turn, results in well-to-well variations in the efficiency with which liquids are withdrawn during the concentration step. Once again, this has the potential of introducing variability and inaccuracy into the assay results. These problems are exacerbated when the cartridge is used for assays which rely upon so-called probe-based nucleic acid hybridization, in which accuracy and sensitivity is even more critical.

Accordingly, a need exists for an improved assay cartridge which is simple in design and relatively easy to manufacture. A need also exists for an assay cartridge which is designed so that a significantly more uniform vacuum draw can be created underneath the wells, thereby improving the reliability and accuracy of assays performed therein. Finally, a need exists for an instrument adapted to be used in combination with such an assay cartridge in performing assays which rely upon nucleic acid hybridization.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide an assay cartridge which is relatively simple in design and easy to manufacture.

It is a further object of this invention to provide an assay cartridge which can be relatively easily and inexpensively molded, but which utilizes a smaller amount of molded material than existing cartridges.

It is a further object of this invention to provide an assay cartridge without an integral waste reservoir and in which a substantially uniform vacuum draw can be created underneath the wells.

It is a further object of this invention to provide associated equipment for use with the assay cartridge, which is designed to uniformly withdraw liquids from the cartridge wells during diagnostic assays.

It is a further object of this invention to provide an assay cartridge and associated equipment which are particularly adapted for use in nucleic acid hybridization assays.

These and other objects are accomplished by providing a cartridge for holding an analytical sample during a diagnostic assay comprising a panel which has a plurality of wells in its upper side. The wells have an upper opening and a lower opening; and the lower opening extends to the underside of the panel. Filter means extend across the lower openings of the wells so that liquids contained in the wells may be drawn through the filter, thereby concentrating suspended solids near the lower openings of the wells. The panel includes a support means for supporting the panel on a non-integral, external surface, which does not form a part of the panel. When placed on a surface, the underside of the panel, the support means, and the surface thereby define a substantially enclosed sub-panel region. When a negative pressure differential is created in the sub-panel region, air is drawn through the wells from the upper side of the

panel, thereby drawing liquid from the wells into the sub-panel region. In a preferred embodiment, the surface supporting the panel is part of an automated or semi-automated instrument designed to perform the various steps of a diagnostic assay sequentially on an amplified or non-amplified nucleic acid target. In this embodiment, the panel is removably attached to the support surface and the support surface can be moved to various positions within the instrument for addition of reagents, removal of liquids from the wells, and the like.

The foregoing features and advantages of the present invention will be more readily understood upon consideration of the following detailed description, taken in conjunction with the accompanying drawings, in which:

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 is an exploded perspective view of an assay cartridge and associated apparatus made in accordance with the present invention;

FIG. 2 is a cross-sectional view of the assay cartridge and associated apparatus in their assembled configuration;

FIG. 3 is a top view of the assay cartridge and associated apparatus in its assembled configuration, including the cartridge locating feature;

FIG. 4 is a cutaway view of an instrument which may be used to perform assays with the cartridge of the present invention; and

FIG. 5 is a perspective view of the front of an instrument which may be used to perform assays with the cartridge of the present invention, showing the cartridge just after it has been loaded into the instrument.

DETAILED DESCRIPTION

Figs. 1 and 2 show the general arrangement of an assay cartridge 10 made in accordance with the present invention. This Specification describes a preferred form of the invention, in which the assay cartridge is used in conjunction with an automated or semi-automated instrument for performing diagnostic assays and, in

particular, probe-based assays. In such an instrument, movement of the cartridge, the addition of reagents to the appropriate wells in the cartridge, as well as the various washing steps, are performed robotically by the instrument. However, it will be understood that the cartridge and associated apparatus of the present invention may also be used to perform such assays manually.

As best seen in Fig. 1, in general the invention includes an assay cartridge in the form of a panel 12, together with associated equipment for drawing liquid reagents through lower openings in the bottoms of the wells 14 in the cartridge. During diagnostic assays, and, in particular assays which utilize nucleic acid hybridization, various liquid reagents and washing solutions are added to the wells 14 in the cartridge 12. Excess reagents and washing solutions can be easily and efficiently removed from the wells using the cartridge and associated apparatus described herein. This apparatus includes a vacuum plate 16 with a vacuum well 17 formed therein and a rubber gasket 18 adapted to maintain an airtight seal between the cartridge 12 and the vacuum plate 16. The vacuum plate 16, in turn, is secured to a base plate 19. The base plate 19 has a channel 20 and a vacuum orifice 22 formed therein. The vacuum orifice 22 is aligned with a corresponding opening 24 in the vacuum plate 16. By creating a negative pressure in the channel 20, a negative pressure differential is also created in the vacuum well 17, thereby causing fluids in the cartridge wells 14 to be drawn by means of the pressure differential into the vacuum well and through the channel 20. The cartridge is preferably inexpensively manufactured so that it can be disposed of after use.

The construction and operation of the cartridge and associated equipment will now be described in further detail. For purposes of this description, the entire disclosures of U.S. Patents Nos. 4,652,533 and 4,704,255, both to Jolley, are incorporated herein by reference and made a part hereof.

Referring simultaneously to Figs. 2 and 3, the assay cartridge of the present invention is a plate or panel 12 having an upper side, an

underside, and a plurality of wells 14 formed therein. The cartridge illustrated takes the general form of a conventional generally rectangular microtitre plate and preferably has either 96 (8 rows of 12) or 48 (8 rows of 6) wells. Each well 14 has an upper opening and a lower opening which extends to the [illegible]side of the panel 12. In the embodiment illustrated, each well 14 takes the form of a generally cylindrical recess formed in the cartridge 12, and tapers at its lower end to a lower opening 26. Alternatively, the wells can be generally parabolic or conical in shape, but truncated at their lower ends to form the lower openings. Each lower opening 26, in turn, is covered with a porous microfilter membrane 28, which is designed to filter and retain suspended solids while permitting unwanted liquids and reagents to pass through. For purposes of the present description, it should be understood that the size, shape, configuration, and method of manufacture of the wells, as well as that of the microfilter, may be as described in U.S. Patent No. 4,704,255.

As best seen in Fig. 2, support means in the form of a supporting wall 30 is formed adjacent the periphery of the cartridge on the underside thereof and extends around the perimeter of the cartridge. This supporting wall 30 has a height greater than the depth of the wells 14 (including the depth of the filter membrane 28) so that the when the cartridge is placed on a flat surface, the lower openings of the wells are elevated above the level of that surface. In a preferred form, the supporting wall 30 also has a substantially flat lower surface, which is adapted to engage a flat surface at substantially all points along the length of the wall. In Fig. 2, the supporting wall 30 is illustrated as a generally rectangular, continuous wall which extends substantially normally from the underside of the cartridge at a position adjacent the peripheral edge of the cartridge. The wall 30 also has a substantially flat lower surface adapted to sealingly engage the flat gasket 18. However, it will be understood that the wall may be formed in any number of ways, as long as the sub-panel region 50 is substantially enclosed so that a negative

pressure may be created therein in order to withdraw fluids from the wells.

In a presently preferred form of the invention illustrated in the drawings, the cartridge is generally open in the sub-panel region 50 (see Fig. 2) beneath the lower openings of the wells. (Although the region is referred to herein as a "sub-panel" region, it will be understood that it need not be located below the panel if, for example, the panel is not supported on a horizontal surface. Thus, this term is meant to encompass any possible orientation of the support surface.) That is, the sub-panel region 50 beneath the lower openings of the wells and interior of the support wall 30 is substantially uncovered at the lower side thereof. In this way, the cartridge may be placed on a generally horizontal surface in order to substantially enclose the sub-panel region such that significant quantities of air may only enter the sub-panel region from the upper side of the panel and through the upper openings of the wells. As described below, means are then provided for creating a negative pressure in this enclosed sub-panel region to withdraw fluids from the wells, through the filter membrane, and into the sub-panel region.

It will also be understood that it may be desirable in certain circumstances to partially cover the bottom of the panel. For example, after liquid from the wells is withdrawn, remnants of the fluid frequently adhere to the underside of the panel. To avoid operator exposure to this fluid, it is sometimes preferred that the bottom of the panel be covered in some manner, for example, by a flexible sheet made of Mylar® or another suitable material, and affixed to the lower surface of the supporting wall. Of course, this covering typically will be partially punctured in some manner when the cartridge is place on the vacuum plate so that a negative pressure may be created in the sub-panel region; however, such a covering will help minimize exposure to any remaining fluid adhering to the underside of the panel.

Additional features of the cartridge will now be described by simultaneous reference to Figs. 1 and 2. In a preferred form, the

panel 12 has a pair of integral ledges 32, 33 (only ledge 32 is visible in Fig. 1) which extend outwardly from the supporting wall 30. If the panel 12 is generally rectangular, as is illustrated in Figs. 1 and 2, ledges 32, 34 are preferably located on the shorter sides of the cartridge and the lower surfaces of the ledges are substantially flush with the lower surface of the supporting wall 30. A pair of V-shaped grooves 34 are formed in the ledge 32 and serve to assist in fixing the position of the cartridge once it is attached to the associated equipment, as will be described in greater detail below. As best seen in Fig. 1, an outside surface of the supporting wall also preferably includes a generally smooth area (which may also be recessed) for receiving an adhesive-backed bar code label 36. The label 36 is used to identify the panel itself or, if the cartridge is being used in a clinical setting, the patient from whom the specimens being tested in the cartridge were taken.

The cartridge may be manufactured by injection molding it in the manner described in U.S. Patent No. 4,704,255. The cartridge of the present invention is unlike that disclosed in the '255 patent, however, in that it lacks, among other things, an intermediate section and an integral waste reservoir. As a result, the cartridge may be molded as a single, integral piece, thereby greatly reducing the complexity and cost of the mold, as well as the amount of molded material required.

Although any number of different materials may be used to mold the cartridge, the material selected should be able to withstand the various temperature cycles encountered during modern diagnostic procedures. The cartridge must also be sufficiently rigid to withstand significant warpage when the wells are evacuated under negative pressure, as will be described in greater detail below. Presently preferred materials which may be used to mold the cartridge include polystyrene, polysulfone, polycarbonate, ABS, polytetrafluoroethylene (PTFE), and polypropylene. To date, success has been had with a butadiene polystyrene bearing the designation 835 and manufactured by Fina of Deer Park, Texas. It will also be understood that the cartridge may be manufactured out of other materials (including

metals) and using other manufacturing methods (such as forming, stamping, and the like).

Filter means in the form of a filter member 28 may be formed as a sheet and positioned so that it extends across and against the lower openings of the wells in any of the ways described in U.S. Patent No. 4,704,255. Preferred filter materials include cellulose acetate, polypropylene, PTFE, and polycarbonate. To date, success has been had with a filter membrane made of cellulose acetate manufactured by Sartorius of Bohemia, Long Island, New York. In a preferred form, a sheet-like filter membrane is joined or attached to the lower edges of the wells which surround the lower openings 26 of the wells 14 by insert molding such that these openings are completely covered by the membrane and liquid cannot leak around the membrane, but must pass through the membrane when it is forcibly evacuated from the wells.

It has been also been discovered that filter membranes having a unique and novel composition may be used to manufacture the cartridges of the present invention, particularly when the cartridge is to be used for probe-based assays. These membranes are comprised of both hydrophilic and hydrophobic materials which have been assembled together in various ways to form an integral membrane. For example, the membrane may be comprised of hydrophilic and hydrophobic layers of filter materials which have been welded together to form a "sandwich." Likewise, the membrane may be a single layer having alternating "strips" of hydrophilic and hydrophobic filter materials. As another alternative construction, the membrane could be comprised of either a hydrophilic or a hydrophobic material with inserts (for example, circular inserts) made of a hydrophobic or hydrophilic material, respectively. These inserts could be dispersed substantially uniformly throughout the membrane.

Other alternative methods of manufacture include manufacturing hydrophobic and hydrophilic materials together, weaving strands of the two types of material together, as well as casting or laminating the two types of material. The specific hydrophilic and hydrophobic

materials which can be used to form such membranes are generally known to those skilled in the art.

Although the way in which such improved membranes function is not completely understood, it is believed they function to disperse the fluids below the wells, thereby reducing variability in the removal of fluids and thus improving the consistency and reliability of the assays performed therein. Such membranes are also believed to prevent cross-contamination between the wells by preventing fluids from migrating across the membrane into other wells.

Referring again to Fig. 1, the manner in which the cartridge 10 works in conjunction with associated evacuating equipment will now be described in greater detail. It should be understood that the cartridge of the present invention is designed to be removably supported on an external surface which is non-integral with the panel itself. That is, the support surface is not attached to, or a part of, the cartridge but, in cooperation with the cartridge, defines the enveloped sub-panel region. Typically, this support surface will be part of a separate instrument in which the panel is used. In a preferred form of the invention, the lower surface of the supporting wall 30 of the panel 12 sealingly engages a gasket 18 resting on a vacuum plate 16 so that unwanted liquids may be removed from the wells 14 by negative air pressure in the sub-panel region. To accomplish this, sealing means in the form of a gasket 18 is interposed between the cartridge 10 and the vacuum plate 16, and downward pressure is exerted on the cartridge 10. In the embodiment depicted in Fig. 1, the gasket 18 is substantially rectangular, open in the area positioned beneath the wells 14, and sufficiently wide so that the bottom surface of the supporting wall 30 can be brought into complete engagement with the gasket at substantially all points along its length. Preferably, the gasket is made of rubber or another compressible material, such as well known polymers or monomers, so that it will provide a substantially airtight seal between the cartridge 12 and the vacuum plate 16 as will now be described.

In a presently preferred form of the invention, the gasket is affixed to the surface of the vacuum plate 16 by means of a suitable adhesive. However, it will be understood that the gasket could be molded (e.g., insert molded) as part of the vacuum plate (if the vacuum plate is molded), or as a separate piece. Likewise, the gasket could be inserted into an appropriately shaped depression in the vacuum plate in an interference fit relationship, or stretched around a lip on the surface of the vacuum plate.

Since the bottom surface of the supporting wall 30 is preferably substantially smooth and relatively flat, downward pressure on the cartridge 12 compresses the gasket 18 and brings the bottom surface of the supporting wall 30 into substantial sealing engagement with it in an interference fit relationship. Although the sealing means is illustrated as a gasket 18 in Fig. 1, it will be understood that it may also take numerous other configurations, such as an O-ring affixed to the inner walls of the well 17 around its periphery, which is adapted to sealably engage the outer surface of the supporting wall 30; a groove around the periphery of the well 17, which is adapted to sealably accept the supporting wall 30 in sealing engagement; a sealing projection, such as a flexible O-ring, on the outer edges of the cartridge itself; or other like configurations.

The vacuum plate 16 is preferably formed of a suitable rigid material, such as aluminum or reinforced plastic, and preferably includes a vacuum well 17 formed in the surface of the plate which faces the underside of the panel 12. However, the plate may be formed of any suitable material, as long as it is sufficiently durable to withstand repeated use. In Fig. 1, the vacuum well 17 is illustrated as a generally wedge-shaped depression in the vacuum plate 16, which is formed by machining. However, it will be understood that the well may take any number of shapes and may be formed by casting, molding, and other well known methods.

An opening 24 through the vacuum well 17 is formed in the vacuum plate 24 by suitable methods, such as drilling, forming, machining, casting, or the like. Preferably, the opening 24 is located

in the deepest area of the well 17, so that gravity will assist in funnelling the liquids to the opening where they are withdrawn under pressure from the well 17. This opening is used to create a negative pressure differential in the sub-panel region, as will be described below. However, it will be understood that this opening could also be located in the panel itself as long as it communicates with the sub-panel region.

It will be understood that a sponge or another absorbent or adsorbent material (not shown) may be placed in the vacuum well 17. The use of such materials assists in efficiently withdrawing fluids from the wells 14 and in preventing an accumulation of fluid on the underside of the cartridge, which is typically undesirable. Alternatively, the well may be formed with a textured interior surface or an integral or non-integral manifold in proximity with the panel which is similarly designed to prevent the accumulation of liquids by channelling them away from the panel.

The vacuum plate 16, in turn, is rigidly mounted to base plate 19 by suitable means, such as screws 40 threaded into corresponding threaded recesses 42 in the base plate 19. The base plate may be formed from the same materials and in the same manner as the vacuum plate. Typically, however, the base plate will be formed of a suitable metal, such as aluminum or reinforced plastic. In a preferred form of the invention to be described hereafter, the base plate 19 forms part of an associated automated or semi-automated instrument, which includes apparatus for moving the plate to various stations for addition of reagents to the wells, incubation, washing, and other processes commonly employed in diagnostic procedures.

It is preferred that the vacuum plate 16 be removably attached to the base plate 19 rather than integrally formed therewith, although the latter is also an acceptable configuration. A removable vacuum plate is preferred so that the vacuum plate 19 may be replaced with another plate sized to accommodate cartridges of varying sizes or shapes. This provides a configuration with a maximum amount of

flexibility to accommodate various currently available cartridges and cartridges which may be developed in the future.

A channel 20 and vacuum orifice 22 is formed in the base plate 19 by machining, casting, molding, or the like. The vacuum orifice 22 is positioned so that it is brought into substantial alignment or registry with the opening 24 in the vacuum plate 16 when the vacuum plate is rigidly attached to the base plate 19. A sealing means, such as an O-ring 44 inserted into a circular groove (not shown) in the base plate 19, is positioned between the vacuum plate 16 and the base plate 19 in the area surrounding the aligned opening 24 and vacuum orifice 22 to substantially prevent leakage of air due to positional tolerances and the like. The channel 20, which communicates with the vacuum orifice 22, is formed in the base plate 19. By connecting the channel 20 through appropriate fittings to a suitable vacuum pump, a negative pressure can be created in the channel 20 and, via the vacuum orifice 22 and opening 24, in the vacuum well 17 located beneath the cartridge wells 14 and, ultimately, in the sub-panel region.

The cartridge 12 is assembled to the vacuum plate 16 in the following manner. Referring simultaneously to Figs. 3 and 4, integral ledge 33 on the panel 12 is positioned under the latch 38. The latch 38 is shaped and positioned to engage the ledge 33 at the adjacent end of the panel 12. (Ledge 33 is similar to the ledge 32 at the other end of the panel 12, except that no grooves 34 need be provided.) The panel 12 is then placed between lateral positioning guides, which may take the form of a pair of stanchions 46a, 46b rigidly attached to the vacuum plate 16 adjacent the long edges of the panel 12 and substantially intermediate their length. The stanchions 46a, 46b help to guide the panel 12 into position so that the V-shaped grooves 34 in the ledge 34 are brought into accepting engagement with the locating guides 48a, 48b, which are rigidly attached to the vacuum plate 16 adjacent the shorter edge of the cartridge 12 opposite the latch 38.

By virtue of such locating means, the cartridge is precisely located with respect to the vacuum plate 16 and the base plate 19. In this regard, it is preferred that the plate be located with sufficient

precision so that the centers of the wells may be located to within .001 inch and, preferably, about .005 inch. This is particularly important when the cartridge is used with an automated or semi-automated instrument, since in order to move the cartridge to appropriate stations so that the appropriate reagents and wash solutions may be dispensed into the correct wells in the cartridge, the location of the cartridge (and, thus, the location of the wells) must be fixed so that it can be known within fairly precise limits.

As best seen in Fig. 4, the latch 38 is preferably slidably attached to the base plate 19 so that it can be moved in a downward direction. In this way, the latch 38 can be mechanically urged (for example, pneumatically or by means of a solenoid) toward the vacuum plate 16 in order to press the lower surface of the supporting wall 30 into an interference fit relationship with the gasket 18, thereby compressing the gasket and forming a substantially airtight seal. Likewise, a similar latch (not shown), either movable or fixed, may be provided at the opposite end of the cartridge to engage the opposite ledge 32 on the cartridge (see Fig. 1) and thereby uniformly hold the other side of the cartridge against the gasket 18.

Referring again to Fig. 2, which shows the panel 12 in its assembled condition, it will be seen that by virtue of the gasket 18 a seal is created around the entire peripheral edge of the panel 12 between the panel and the vacuum plate 16. This, in turn, creates a substantially enclosed sub-panel volume V comprised of the sub-panel region 50 beneath the wells 14 and membrane 28 and interior of the supporting wall 30, together with the area in the vacuum well 17. This is a significant feature of the present invention, since an associated vacuum pump P can be connected to the volume V via the channel 20 and aligned vacuum orifice 22 and opening 24. Upon actuation of pump P, a substantially uniform negative pressure can be created in the volume V beneath the wells 14. By creating such a uniform or consistent pressure beneath the wells which does not vary significantly from well to well, the disadvantages of non-uniform vacuum draw described above are significantly reduced, thus improving the consistency and accuracy of assays performed in the

cartridge. (As noted above, a negative pressure may also be created through an opening in the panel itself which communicates with the sub-panel region; however, a special connection between the pump P and the panel would be required to accomplish this.)

It will be understood that the pump P should be operated at pressures which efficiently and substantially remove liquids from the panel wells 14 in order to effectively concentrate the solids remaining in the wells near the bottom openings of the wells. While such pressures may be readily selected and optimized by those skilled in the art depending on the configuration of the entire system, in many applications such pressures will be approximately 22 inches of mercury or greater.

Figs. 4 and 5 illustrate schematically an instrument which may be used to mechanically manipulate the cartridge in order to move the wells to and from various stations for dispensing reagents and the like during the course of performing a diagnostic assay. As best seen in Fig. 4, the instrument 60 includes means for moving the base plate 19, together with the attached vacuum plate 16 and panel 12, to substantially all locations within a plane which is parallel to the planes of the base plate 19, vacuum plate 16 and panel 12, but perpendicular to the face of the instrument.

This is accomplished by means of a pair of lead screws 62a, 62b, which are rigidly attached to the base plate 19 and powered by motors 64a, 64b. These motors may be stepper motors, servo motors, or the like. The motors 64a, 64b, in turn, are under the control of a central processor (not shown) which, in response to input from the instrument operator, as well as other internal inputs, actuates the motors to power the lead screws 62a, 62b and thereby position the cartridge in the desired location within the instrument. It will be seen that lead screw 62a is adapted to move the base plate 19 in a first or "X" direction, while lead screw 62b moves the base plate 19 in a second or "Y" direction substantially perpendicular thereto. It will be seen that by sequential actuation of the motors 64a, 64b, base plate 19 may be moved to precisely defined Cartesian coordinates

within the plane of motion, thereby positioning the panel 12 and its wells 14 in desired locations within the instrument so that reagents may be dispensed into selected wells at appropriate times during the course of a diagnostic assay.

Fig. 5 illustrates the position of the cartridge just after it is loaded into the instrument 60 or just prior to the time it is removed from the instrument. By actuating motors 64a, 64b, the base plate 19 and attached vacuum plate 16 are brought into alignment with slot 66 in the front face of the instrument 60. Motor 64b is then actuated to move the base plate 19 through the slot such that the cartridge is brought outside the body of the instrument. Upon release of the latch 38, the cartridge may be manually inserted into, or removed from its fixed position on the vacuum plate 16. Typically, the cartridge is inserted prior to the start of the assay and removed after the assay is completed, although it will be understood that it may be desirable to remove the cartridge during the course of the assay for addition of reagents and the like.

The operation of the instrument will now be described in detail. In response to a command from the operator, motors 64a, 64b are actuated to position the base plate 19 and attached vacuum plate 16 in the general position shown in Fig. 5. The operator then attaches a panel 12 to the vacuum plate 16 in sealing engagement with the gasket in the proper position, being guided by the locating guides on the vacuum plate 16, as described above. Prior to attachment of the panel 12, one or more wells 14 are inoculated with an appropriate sample -- for example, a sample of a bodily fluid which has or has not been subjected to nucleic acid amplification.

Motors 64a, 64b are then actuated to bring the cartridge into the body of the instrument 60 and to move the appropriate well(s) into alignment with various dispensing or incubating stations, where appropriate detection and washing reagents are dispensed into the wells. At an appropriate time during the process, pump P (see Fig. 2) is actuated in order to create a negative pressure in the sub-panel region beneath the wells 14. This negative pressure differential

uniformly draws fluids in the wells 14 into the vacuum well 17 and out through the opening 24 and the vacuum orifice 22. At this point, the fluids are drawn through the channel 20 in the base plate 19 and, preferably, into a waste container (not shown) for safe disposal. The solids which have been concentrated on the membrane at the lower ends of the wells 14 can then be analyzed through well-known detection methods, such as fluorometry, spectrophotometry, radiometry, and the like. (See, for example, the detection methods described in U.S. Patent No. 4,652,533.)

While the invention has been described in connection with certain presently preferred components and arrangements, those skilled in the art will recognize many modifications to structure, arrangement, portions, elements, materials, steps, and components which can be used in the practice of the invention without departing from the principles thereof.

CLAIMS

WHAT IS CLAIMED IS:

1. A cartridge for holding an analytical sample during a diagnostic assay comprising:

a panel having an upper side and an underside, said panel having a plurality of wells in its upper side, each well having an upper opening and a lower opening which extends to the underside of the panel,

filter means extending across the lower openings of the wells, and

said panel further including support means for supporting the panel on an external surface which is non-integral with the panel such that the underside of the panel, the support means, and the surface define a substantially enclosed sub-panel region when the panel is placed on the surface, and said panel being adapted to sealingly engage the surface such that when a negative pressure differential is created in the sub-panel region air is drawn through the wells from the upper side of the panel, thereby drawing liquid in the wells into the sub-panel region.

2. The cartridge of claim 1 wherein the support means comprises a continuous wall adjacent the periphery of the panel, said wall having a substantially flat lower surface adapted to engage a generally flat surface.

3. The cartridge of claim 2 wherein the panel is generally rectangular in shape and wherein the continuous wall projects substantially normally from the underside of the panel.

4. The cartridge of claim 1 wherein the filter means comprises a substantially flat sheet which is affixed to the underside of the panel.

5. A cartridge for holding an analytical sample during a diagnostic assay comprising:

a generally rectangular panel having an upper side and an underside, said panel having a plurality of wells in its upper side, each

well having an upper opening and a lower opening which extends to the underside of the panel,

filter means extending across the lower openings of the wells, and

said panel further including a substantially continuous support wall adjacent the periphery of the panel and projecting substantially normally from the underside of the panel for supporting the panel on a generally flat surface such that the filter means, the support means, and the surface define a substantially enclosed sub-panel region when the panel is placed on the surface, and said panel being adapted to sealingly engage the surface such that when a negative pressure differential is created in the sub-panel region air is drawn through the wells from the upper side of the panel, thereby drawing liquid in the wells into the sub-panel region.

6. An instrument for holding and processing analytical samples during a diagnostic assay comprising:

a support surface,

a cartridge removably supported on the support surface, said cartridge including

(a) a panel having an upper side and an underside, said panel having a plurality of wells in its upper side, each well having an upper opening and a lower opening which extends to the underside of the panel,

(b) filter means extending across the lower openings of the wells, and

(c) said panel further including support means for supporting the panel on the support surface;

said filter means, said support means and said support surface defining a substantially enclosed sub-panel region; and

sealing means interposed between the support means and the support surface for effecting a substantially airtight seal between the support means and the support surface.

7. The instrument of claim 6 wherein the support means comprises a continuous wall adjacent the periphery of the panel, said wall having a substantially flat lower surface adapted to engage a generally flat surface.

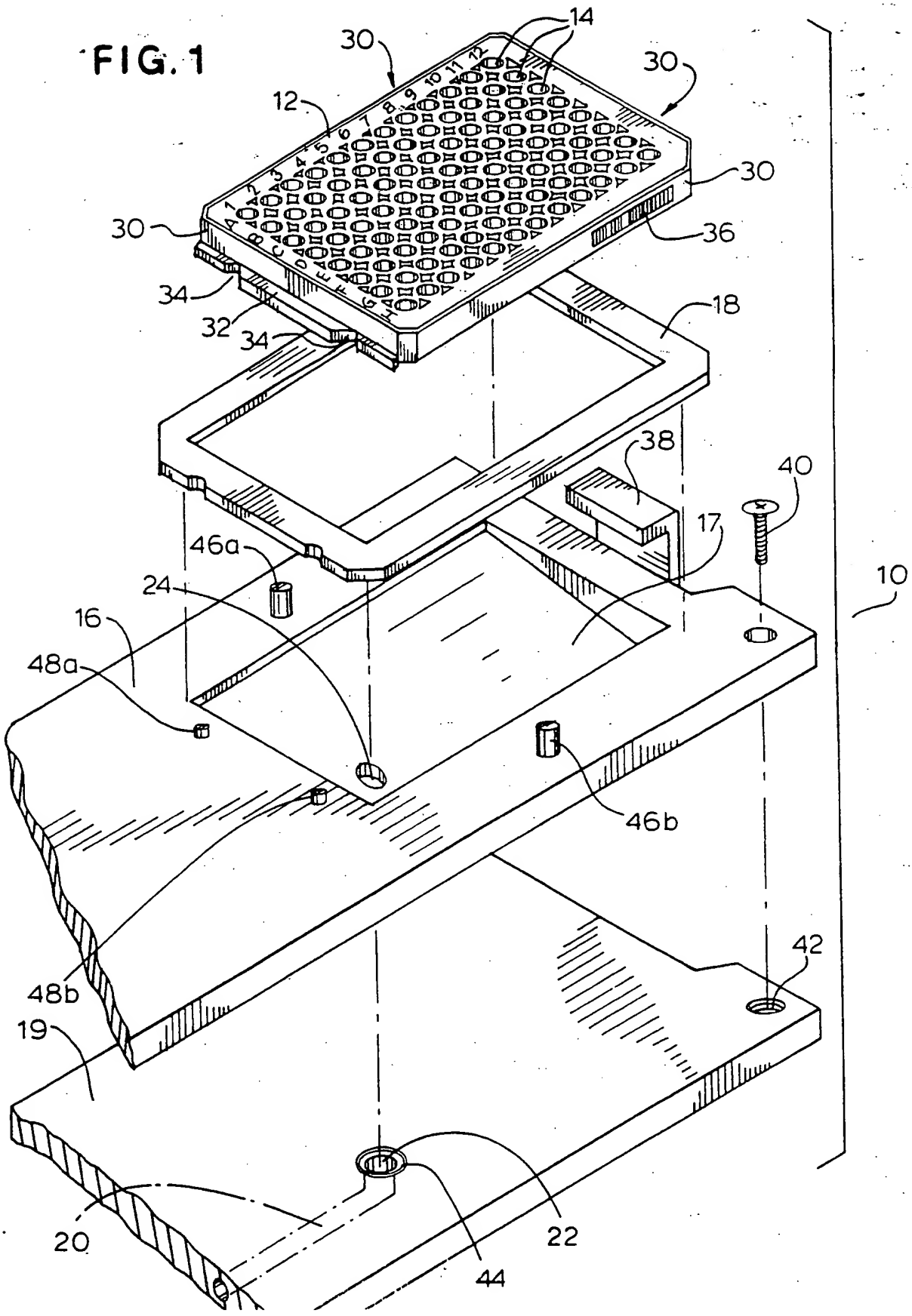
8. The instrument of claim 7 wherein the panel is generally rectangular in shape and wherein the continuous wall projects substantially normally from the underside of the panel.

9. The instrument of claim 6 wherein the filter means comprises a substantially flat sheet which is affixed to the underside of the panel.

10. The instrument of claim 6 further comprising pump means for reducing the pressure in the sub-panel volume, said pump means being in communication with the sub-panel volume through an opening formed in the support surface, said pump means being adapted to draw fluid in the wells through the filter means by reducing the pressure in the sub-panel region.

11. The instrument of claim 6 further comprising locating means on the support surface for fixing the position of the panel on the support surface.

FIG. 1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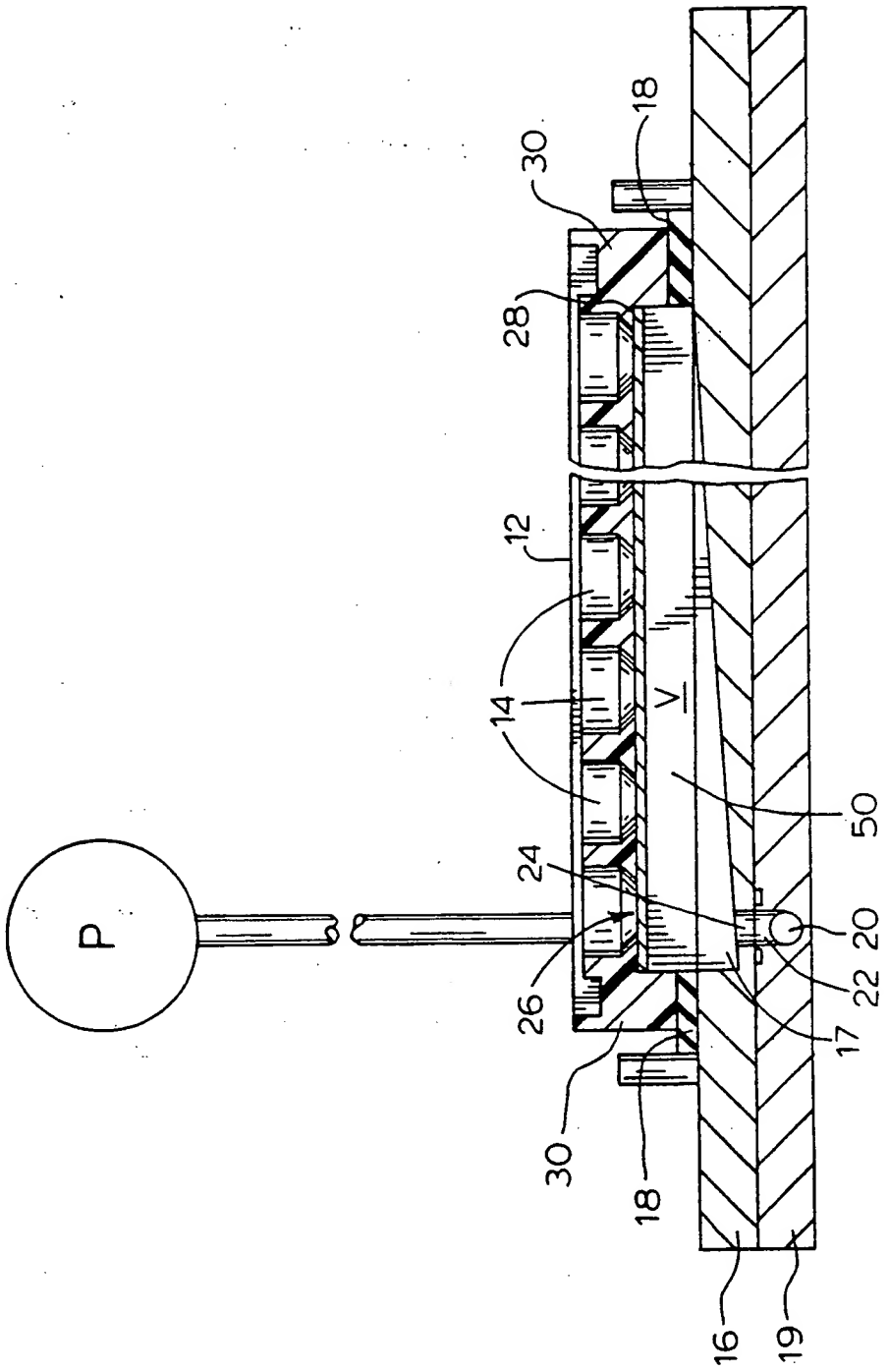

FIG. 2

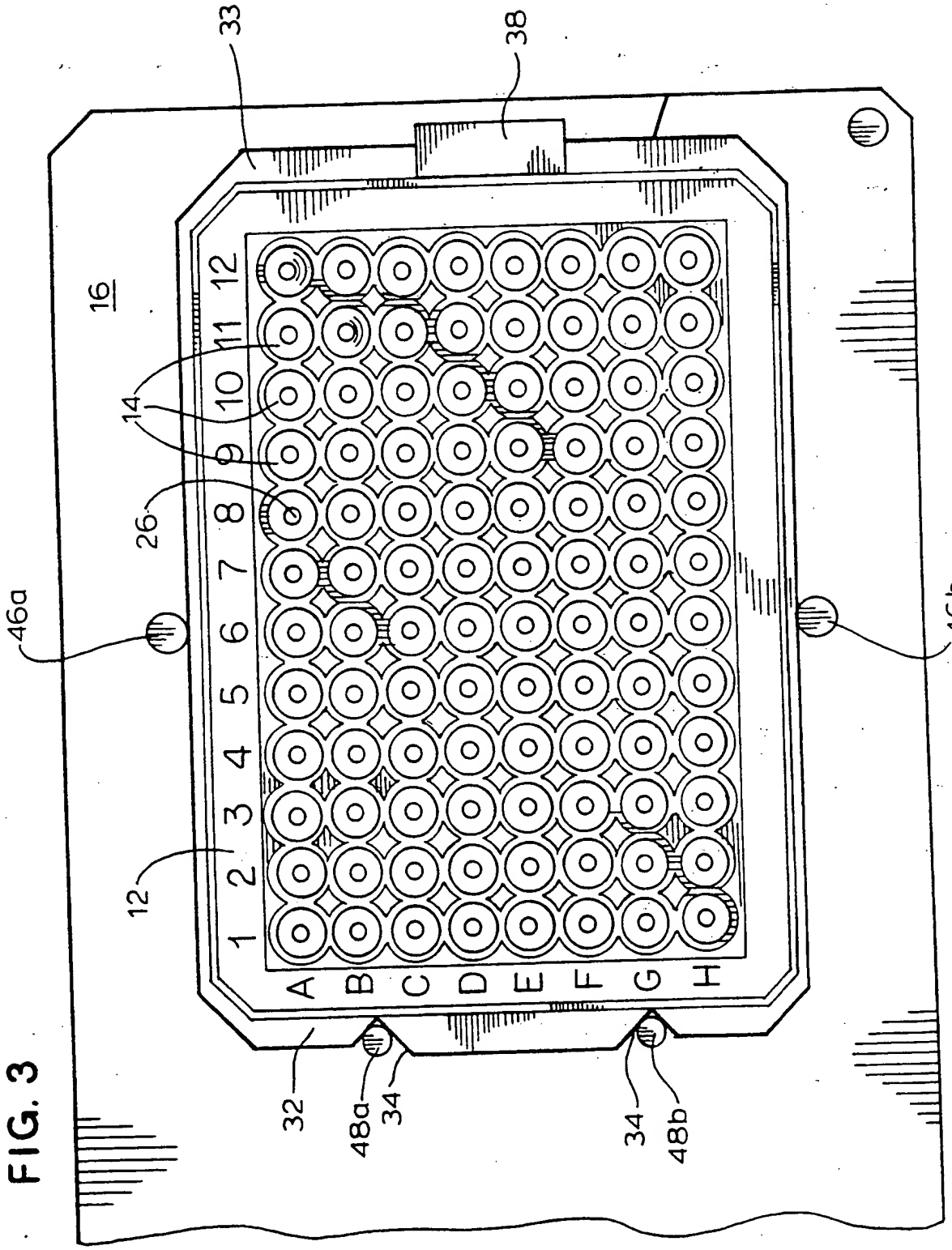
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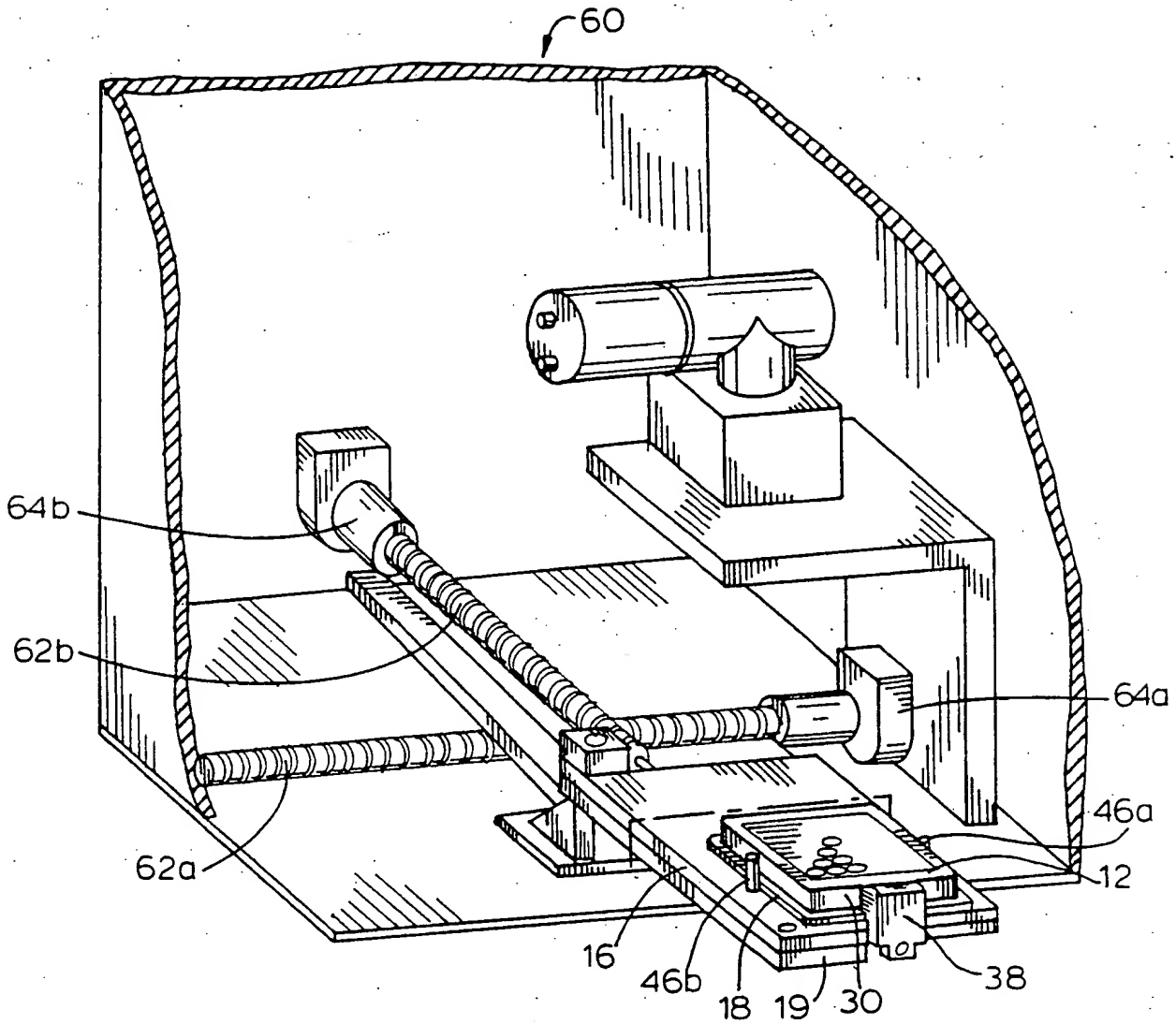
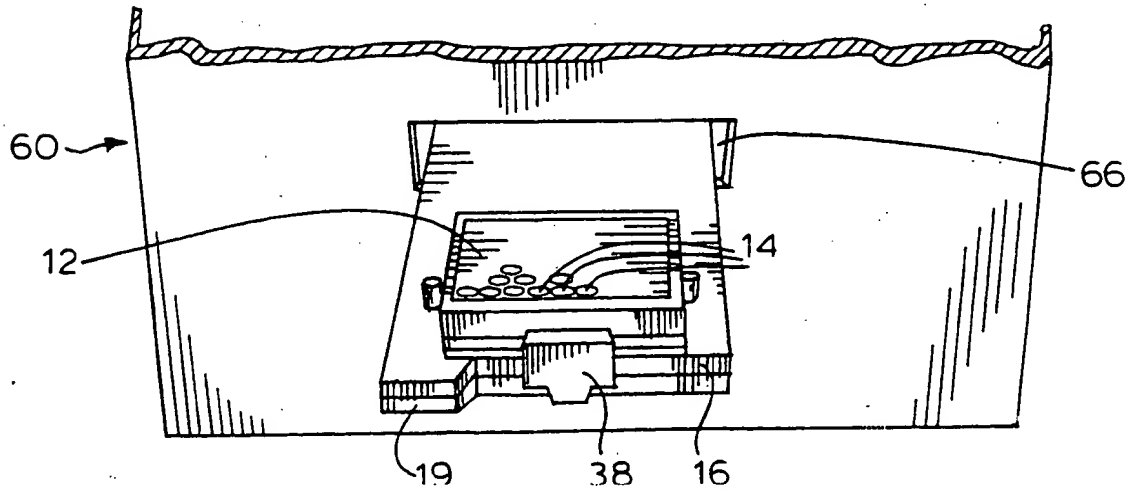
FIG. 3

FIG. 4





INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/09395

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :B01L 3/00
US CL :422/101, 102; 436/177
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 422/58, 99, 101, 102; 436/177

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 4,704,255 (JOLLEY) 03 NOVEMBER 1987, see entire document.	1-11
A	US, A, 4,948,442 (MANNS) 14 AUGUST 1990, see entire document.	1-11
Y	US, A, 4,890,930 (NOHSO) 02 JANUARY 1990, see entire document.	1-11
A	US, A, 5,061,452 (YAMAMOTO ET AL) 29 OCTOBER 1991, see entire document.	1-11
A	US, A, 3,649,464 (FREEMAN) 14 MARCH 1972, see entire document.	1-11

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date		
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search 30 December 1993	Date of mailing of the international search report JAN 27 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks	Authorized officer

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/09395

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4,154,795 (THORNE) 15 MAY 1979, see entire document.	1-11
A	US, A, 4,167,875 (MEAKIN) 18 SEPTEMBER 1979, see entire document.	1-11
A	US, A, Re. 30,562 (PARK) 31 MARCH 1981, see entire document,	1-11
A,P	US, A, Re. 34,133 (THORNE) 24 NOVEMBER 1992, see entire document.	1-11
A,P	US, A, 5,171,533 (FINE ET AL) 15 DECEMBER 1992, see entire document.	1-11
A,P	US, A, 5,167,922 (LONG) 01 DECEMBER 1992, see entire document.	1-11
A	US, A, 5,039,493 (OPRANDY) 13 August 1991, see entire document.	1-11